T cells but not with normal human peripheral B cells, null cells, or macrophages;

vii) transferring said clones intraperitoneally into mice; and

viii) harvesting the malignant ascites or serum from said mice, which ascites or serum contains the desired antibody.

REMARKS

Reconsideration is respectfully requested.

A. Amendments

Claims 1 and 17 have been amended, Claim 4 has been cancelled and rewritten as Claim 22, and new method Claims 23-26 are presented. Support for the amendments to Claims 1 and 17 is found in the claims as filed and also in the specification at page 8 (for Claim 1) and on page 10, line 26, through page 11, line 11 (for Claim 17). Support for new Claim 22 is found in the specification at page 6, line 32, through page 7, line 16. Support for new method Claims 23-26 is found in the specification at page 10, line 1, through page 16, line 35.

Additionally, unelected claims 5-14 and 19-21 have been cancelled without prejudice to their presentation in a subsequent divisional application.

B. The Interview

The kindness of Examiner Fagelson in granting an interview with Applicants and their Attorney on May 29, 1980, is gratefully acknowledged. During the course of this inter-

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view, the Applicants and their Attorney discussed with the Examiner the issues presented by the outstanding Official Action in this application and certain of their other co-pending applications relating to monoclonal antibody inventions. During the interview, agreement was reached with regard to the claims presently under consideration. The Examiner stated that she would allow the claims if they were amended in accordance with the points discussed at the interview to clarify the claims to the antibodies. It is believed that the amendments to Claims 1 and 17 and the revision of Claim 4 achieve this result. Additionally, it is believed that newly presented method Claims 23-26 are also allowable, which claims recite methods of preparing the subject antibody.

During the interview, Applicants and their Attorney presented a discussion of what was generally known in the relevant arts prior to the present invention. The following is a summary of that discussion.

Cell surface antigens are markers on cell surfaces by means which of cells may be recognized. Some of these antigens define particular classes of cells for all members of a species; these are called differentiation antigens. There are also many other types of antigens which define (e.g.) a particular individual or strain, a particular sex, a particular species, or the like. For example, much work has been done on so-called HLA antigens, which are present on almost all cells of a given individual.

Before the present invention, cell surface antigens had been studied principally in the mouse by raising alloantibodies in one strain or individual by injection of cells from a different strain or individual. These alloantibodies

were strain- or individual-specific and did not relate to specific classes of cells. Little was known about differentiation antigens in any species, let alone humans, although there was considerable interest in the subject.

It was also recognized that one could not predict the antigen system in one species of animal (e.g., man) from work in another species (e.g., the mouse), nor could one predict cell surface antigens on normal cells from work with malignant cells or transformed cell lines.

In addition to this knowledge regarding cell surface antigens, there was also a body of information regarding hybrid cell techdniques, of which the Melchers reference discussed below is a good example. There techniques were generally known in the same way that techniques of organic synthesis are known, as general methods for preparation of certain types of products.

C. Rejection Under 35 USC 112 (Second paragraph)

In view of the amendments recited above, it is believed that the rejection of Claims 1-4 and 17 under 35 USC 112 (second paragraph) is now moot. The confusion regarding the antigen has been removed from Claim 1. Claim 17 now recites antibody production and has been amended to remove a step erroneously included in the claim as filed. Claim 4 has been cancelled and replaced by Claim 21.

D. Double Patenting Rejection

This rejection of Claims 1-4 and 15-18 is respectfully traversed. First, the claims are not exact duplicates of those in Serial No. 022,132 for reasons set out below. Hence, this rejection is interpreted to be one for

"obviousness-type" double patenting. Since Claim 4 has been cancelled and new Claims 23-26 have been added, these remarks will be directed to all outstanding claims.

The present application discloses and claims a complement-fixing mouse monoclonal antibody which is specific to an antigen on essentially all normal human peripheral T cells. The subject antibody does not distinguish one subclass of T cells from another but rather identifies all T cells. Product Claims 1-3 and 21 and method Claims 15-18 and 23-26 all point out thess characteristics.

While the subject claims are similar to those of copending application Serial No. 022,132, they are distinct in the recitation of the complement-fixing property. It is respectfully submitted that this additional recited property renders the subject claims patentably distinct from those of the '132 application.

The subject claims are also believed patentably distinct from the claims of other copending applications of the same Applicants relating to monoclonal antibody inventions. For the Examiner's assistance, a summary of these applications pointing out the differences is attached hereto as Exhibit I.

E. Rejection Under 35 USC 103

The final issue remaining from the Official Action is the rejection of Claims 1-4 and 15-18 as being obvious in view of references L plus N plus P plus O plus Y in view of X. The Examiner has asserted that no patentable merit is seen in employing the known hybridoma means taught by L, Y, and O and selecting predetermined antibodies according to desired characteristics. The Examiner has stated that the

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use of a T cell as antigen is clearly indicated by these references.

First, none of these references teach or even suggest the preparation of a monoclonal antibody which specifically reacts with a differentiation antigen on a defined class or subclass of normal human T cells. The references disclose, on the contrary, antibodies which display undefined patterns of reactivity, generally to malignant cell lines or to cells from other strains of mice or from rats.

Reference L (Melchers) is a general discussion of techniques and contains no specific teaching or suggestion regarding the present invention.

Reference N (Trucco) teaches the immunization of mice with a human lymphoblastoid cell line and screening with the same and other lines to obtain alloantibodies or antibodies having variable patterns of reactivity. No antibody was produced which is specific for a defined class or subclass of cell. Trucco in no way suggests the subject antibody or methods.

Reference O (Levy) teaches the immunization of mice with human leukemia cells or cell lines and screening with leukemia cells, cell lines and peripheral blood lymphocytes At page 167 and 168 he indicates the general lack of succes experienced. Moreover, Levy in no way suggests the use of normal human T cells for both immunization and screening, as done in the subject invention.

Reference P (Hammerling) teaches the immunization of one strain of mice with spleen cells from other strains of mice to obtain alloantibodies to mouse cell surface antigens. There is also disclosure of immunizing rats with mouse T

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lymphoma cells. In view of the previous discussion, this reference is remote from the invention claimed herein.

Reference Y (White) teaches the immunization of mice with rat thymocyte membrane. Not only does White not suggest the preparation of antibodies to human cells, but he also indicates in the lower part of page 671 his lack of practical result.

Reference X (Fox) is an article in a lay publication which adds nothing to the other references.

Thus, none of these references, either alone or in combination, teach or suggest the claimed antibody or methods of preparation.

Second, the references do not teach a "known hybridoma means" since each hybrid cell is a function of the two cells which make it up - the myeloma cell and the spleen cell from the immunized mouse. And, of course, the latter depends upon the material used for immunization. As described above, none of the references suggest the type of immunization or screening used herein, and thus none suggest the present invention.

As explained during the interview, references L, N, O, P, and Y do not teach the use of a purified normal human T cell for immunization but instead teach at best the use of a malignant human T cell line or leukemia cell. The use of cell lines for immunization was found by the present Applicants not to produce the claimed hybrid cell, which confirmed the lack of success referred to in the art.

Finally, it is respectfully submitted that the cited references are actually evidence of the unobviousness of the present invention. Dispite the interest in preparing monoclonal antibody similar to that of the present appli-

cation, the cited references and others show a uniform lack of success in achieving this goal. That Applicants have succeeded where others have failed is surely good evidence of the unobviousness of the present invention.

F. Conclusion

For the reasons presented above, it is respectfully submitted that Claims 1-3, 15-18, and 22-26, all those presently in the application, are allowable. Accordingly, withdrawal of the outstanding rejections and allowance of the claims are earnestly solicited.

Respectfully submitted,

Geoffrey G. Dellenbaugh
Attorney for Applicants
Registration No. 26,864

GGD/jt

501 George Street
New Brunswick, N.J. 08903
(201) 524-9323

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D. C. 20231, on July 11, 1980
(Date of Deposit)

Geoffrey G. Dellenbaugh
Name of applicant, assignee, or Registered Representative

(Signature)

July 11, 1980
(Date of Signature)

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Exhibit I

Attorney Docket No.	Serial No.	Antibody Characteristics
ORTH 336	22,132	Identifies all normal human peripheral T cells
ORTH 344	33,639	Identifies all normal human helper T cells, a subclass comprising about 55% of normal human peripheral T cells.
ORTH 345	33,669	Identifies all normal human peripheral T cells. Fixes complement.
ORTH 353	76,642	Identifies normal human cytotoxic and suppressor TH_2^+ T cells, a subclass comprising about 20% of normal human peripheral T cells.
ORTH 355	82,515	C-I-P Application of SN 76,642
ORTH 357	99,970	Identifies about 70% of normal human thymocytes, which are precursors of T cells. Does not react with normal human peripheral T cells, B cells, or null cells.
ORTH 358	99,969	Identifies normal human suppressor T cells, a subclass comprising about 30% of normal human peripheral T cells. Also reacts with about 80% of normal human thymocytes but not with normal human peripheral B cells or null cells.
ORTH 359	100,071	Identifies normal human early thymocytes, a subclass comprising about 10% of normal human thymocytes. Does not react with normal human peripheral T cells, B cells, or null cells.
ORTH 360	100,072	Identifies normal human prothymocytes, a subclass comprising about 95% of normal human thymocytes.